

**IN THE UNITED STATES DISTRICT COURT FOR THE  
MIDDLE DISTRICT OF TENNESSEE  
NASHVILLE DIVISION**

RUTH SMITH, Individually and as Widow for the )  
Use and Benefit of Herself and the Next of Kin of )  
Richard Smith, Deceased, )  
Plaintiff, )  
v. ) Civil No. 3:05-0444  
PFIZER INC., *et al.*, ) Judge Aleta A. Trauger  
Defendants. )

**TESTIMONY OF JANET ARROWSMITH, M.D.**

My name is Janet Arrowsmith. I live in Ruidoso, New Mexico. I am a physician licensed to practice in the state of New Mexico. I am board certified in Internal Medicine, an elected member of the American College of Epidemiology, and an elected Fellow of the American College of Physicians. I received my undergraduate degree at Duke University in 1972 and obtained my medical degree from Tulane University School of Medicine in 1979.

I have 11 years of experience with the United States Food and Drug Administration (FDA). From 1984-1986, I was an Epidemic Intelligence Service Officer at the National Centers for Disease Control (CDC) and Prevention in Atlanta, Georgia. In this position, I participated in CDC and FDA epidemiologic investigations of problems of national and regional interest. From 1986-1988, I served as a Staff Epidemiologist in the Office of Epidemiology and Biostatistics at the FDA. In this position, I monitored the postmarket safety of marketed drugs, and I served as a consultant to the Centers for Drugs and Biologics Evaluation and Research on epidemiologic issues and problems. From 1988-1990, I was the Deputy Director for Office of AIDS and Special Health Concerns. From 1990-1991, I was the Senior Medical Officer for HIV at the

Agency for Healthcare Policy and Research. From 1991-1993, I was a Medical Review Officer in the Division of Antiviral Drug Products in the Center for Drug Evaluation and Research (CDER). From 1993-1995, I was the Acting Director of the Office of Surveillance and Biometrics in the Center for Devices and Radiological Health at the FDA. From 1995-1996, I was a Medical Review Officer in the Division of Blood Applications, Office of Blood Research and Review in the FDA Center for Biologics Evaluation and Research. In both of my positions as a Medical Review Officer, I was responsible for reviewing premarket INDs and NDAs. I was on the faculty at Georgetown Medical Center in D.C. from 1986-1996 while I was at FDA and had an afternoon clinic with residents where I provided clinical oversight for several years. I also provided primary care in a community HIV/AIDS clinic in D.C. (at the time the largest AIDS community-based clinic in the country) for eight years. After I left FDA and Washington, D.C., I remained with the Public Health Service and moved to New Mexico, where I was assigned to the Indian Health Service and was a primary care provider in the Mescalero Apache Hospital on the Mescalero Apache Reservation near Ruidoso. A copy of my resume includes my educational and professional experience and is marked as **Exhibit 7426. [SHOW POWERPOINT HERE (DR. ARROWSMITH'S QUALIFICATIONS)]**

In my clinical practice, I have prescribed medicines “off-label” countless times. Off-label means uses other than those for which the medication has specific approval. The off-label use of medicines is part of the practice of medicine. It is part of the standard medical training and experience a doctor receives during medical school and residency. As you go into practice, you gain experience with the off-label use of medicines as a matter of routine clinical practice. Examples of medicines that I’ve prescribed off-label include: anticonvulsants, such as Neurontin and Dilantin, for neuropathic pain; antidepressants, including tricyclic antidepressants for

neuropathic pain and fibromyalgia; antibiotics for children; and beta-blockers and ACE inhibitors for heart failure.

My opinions are expressed to a reasonable degree of medical and scientific certainty, and are based on my training and experience as a medical doctor, epidemiologist, FDA medical review officer and acting director of Office of Surveillance and Biometrics. My opinions are also based on my knowledge of the regulations under which drug development occurs in the U.S. under which pharmaceutical manufacturers are required to operate. These regulations are based on the Federal Food, Drug, and Cosmetic Act. My opinions are also based on my knowledge of and experience with FDA policies and procedures, as well as industry practices with which I have become familiar through my employment at FDA and my consulting experience. My opinions are summarized as follows: **[SHOW POWERPOINT HERE (SUMMARY OF DR. ARROWSMITH'S OPINIONS)]**

- (1) The Neurontin labeling was adequate under the regulations and provided appropriate information for safe and effective use.
- (2) The package insert, and the Investigator's Brochure prior to approval, included information concerning suicidal behavior and adverse effects on mood reported during clinical testing.
- (3) There was no reason for Pfizer to warn of suicidal behavior in the Neurontin labeling prior to the requirement of class labeling in 2009 as the available information did not establish that this medicine was associated with an increased risk of suicidal behavior.

I have reviewed a substantial number of documents relating to Neurontin. These documents include, but are not limited to, documents from the Neurontin IND, NDA and

sNDAs; the FDA medical officer's reviews of the NDAs and sNDAs; Neurontin labeling; the September 13, 2007 affidavit of Cynthia McCormick, M.D., the FDA medical review officer who reviewed the initial NDA for Neuron ; documents relating to contacts between FDA and the sponsor, including the company's ongoing evaluations of the potential risks of suicide and depression; internal FDA documents; the 2008 Advisory Committee transcript and supporting documents; regulations in 21 CFR part 300, which were in effect during the time Neurontin was under development and throughout its marketing history; as well as relevant journal articles and other scientific publications. I rely on my professional training and experience in assessing the materials I have reviewed. In addition, I have reviewed the expert reports, deposition testimony, and materials considered by plaintiffs' expert Cheryl D. Blume, Ph.D. I have also reviewed expert reports and materials considered by other defense experts.

To begin with, I would like to describe what the Food and Drug Administration (FDA) is and what it does. The FDA is the expert federal agency charged by Congress with ensuring that prescription drugs for the U.S. market are "safe and effective" when used in accordance with the approved product labeling. FDA's authority to regulate the manufacture, labeling and distribution of human medicines is aimed at promoting and protecting the public health. The primary focus of FDA is patient and public health safety. FDA regulations governing drug development, labeling, and marketing establish both a 'floor' and a 'ceiling' for safety. Given the comprehensiveness of FDA regulation of drug safety, effectiveness, and labeling under the act, additional requirements for risk disclosure are not necessarily more protective of patients. Exaggeration of risk could discourage appropriate uses of a beneficial drug.

The FDA has over 9,000 employees located in more than 150 U.S. cities. Among its staff, FDA has several thousand scientists, including physicians, chemists, pharmacologists,

epidemiologists, statisticians, microbiologists and other professionals. Many of these scientists work in CDER (Center for Drug Evaluation and Research), the drug review, approval and monitoring section of the FDA. CDER is the largest drug regulatory agency in the world.

In this case, there has been extensive dialogue and exchange of information between FDA and Pfizer concerning the safety of Neurontin. As I will explain later, at no time did FDA require a warning concerning depression or suicide based upon the Neurontin data alone. The class warning about suicidal behavior came about following FDA's 2008 combined analysis of clinical trials data for 11 antiepileptic drugs. Because of the data included in this analysis, only FDA could perform the analysis and only FDA can impose a class label.

Since 1962, federal law requires pharmaceutical companies to submit to FDA for its review an Investigational New Drug application (IND) prior to administering an unapproved drug to humans in the U.S. The IND contains extensive information on the manufacture of the drug, animal studies, pharmacologic studies, and protocols for the first studies in humans.

Assuming FDA permits the IND to go forward, both FDA and the manufacturer will monitor results and safety data from the clinical trials. As a practical matter, drug product sponsors usually request formal meetings with the FDA review division responsible for the IND to discuss essential aspects of the drug development plan. Typically, there may be a pre-IND meeting, an End-of-Phase 2 meeting and other meetings between representatives from the sponsor and FDA management and review scientists. In these meetings, the sponsor proposes a development plan, receives advice from FDA scientists, and may seek agreement on specific aspects of the drug development plan.

Assuming that clinical drug development progresses to the point that the sponsor believes there is sufficient data to demonstrate safety and effectiveness of the drug for a specific

indication, it can submit a New Drug Application (or NDA) to FDA, requesting permission to market the drug in the U.S. The content and order of information in the NDA are established by FDA regulations and includes, among other things, detailed descriptions of a) pre-clinical pharmacology and toxicology studies concerning the drug and its possible side effects; b) human pharmacokinetics and bioavailability studies concerning the drug; c) clinical studies establishing the safety and effectiveness of the drug; d) statistical analyses of clinical and preclinical studies; and e) draft product labeling. Approval of a new drug for marketing includes FDA approval of the labeling. Applications for approval to market a drug for additional indications after the initial product approval are submitted in supplemental New Drug Applications, or sNDAs.

Once the NDA has been submitted, FDA scientists determine whether the data are sufficient to establish that the drug meets FDA's safety and efficacy requirements. A team of physicians and other scientists conduct a careful review of the NDA and prepares detailed reports on their findings. FDA reviewers are all experts in their fields. After intensive assessment by the FDA review team, FDA makes a decision about the NDA. At the time of the initial approval of Neurontin, FDA issued letters to sponsors indicating that the NDA was approved, not approved, or was approvable. If the NDA was approvable but not approved, FDA identified the deficiencies that must be corrected and the additional information that must be submitted before approval would be reconsidered.

The U.S. drug development process is rigorous and scientifically sound. FDA estimates that of the thousands of compounds initially identified as having potential a new human drug, only five will enter clinical testing; of those five, three will result in an NDA, but only one will eventually be marketed.

A prescription drug label is the primary way FDA and the manufacturer communicate essential information for safe and effective use of the drug to prescribers. FDA carefully controls the content of labeling of prescription drugs. Both the manufacturer and FDA continuously monitor the available scientific information on the safety of products in order to incorporate important new information into product labeling when appropriate.

Draft labeling is submitted as part of every NDA. The draft labeling is extensively reviewed and revised by the sponsor and by FDA prior to approval. Development of the product label is a lengthy process and typically involves extensive communications between the company and FDA. FDA has full authority over each section of the label and FDA makes the final determination on the appearance, content, placement and language for information included in the label. The final draft of a product label is the product of the best judgment of both the manufacturer and FDA and in accordance with the regulations. Both FDA and the product sponsor review the labeling throughout marketing for possible revisions based on postmarketing safety data or other information. As I understand in the *Smith* case, the issue involves whether the label should have included a warning about an increased risk of suicidal behavior or depression. At no time during the relevant time period did FDA request, nor did the available information require, that the Neurontin label include a specific warning about suicidal behavior or depression. It is my opinion that the available data do not establish that Neurontin is associated with an increased risk of suicidal behavior and that FDA's decisions concerning the Neurontin label prior to the imposition of a class wide label in 2009 were appropriate.

Specifically, the labeling requirements in effect during the relevant time period are found in 21 C.F.R. § 201.57. These requirements specified that safety information was to be included in the Contraindications, Warnings, Precautions, and Adverse Events sections of the labeling.

These FDA regulations established when a warning needed to be included in a label, stating that “The labeling must be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved.”

**[SHOW POWERPOINT HERE (21 C.F.R. 201.57 (2002))]** If the evidence for a particular adverse event does not rise to the level of “reasonable evidence of an association,” there is still a place in the label for reporting that event. One section is the “Clinical Trials Experience” section, where the company lists adverse reactions reported from clinical trials. Including an adverse event in this section does not mean the company or FDA has concluded that the event occurred as a result of the drug, but rather that these events have been observed at certain rates in the clinical trials data set.

FDA also has authority to require certain labeling changes when a drug such as Neurontin is being prescribed used off-label. Specifically, FDA can require a labeling change or warning if the off-label use is not effective or if the off-label use poses a significant risk or hazard. Here is what the regulations provide. Under 21 C.F.R. § 201.57(c) (2005) “[i]f there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows the drug is ineffective” FDA may require that the label state that there is a lack of evidence demonstrating efficacy for that use. In the recently published revisions to the format for prescription drug labels, FDA may require the addition of warnings to a package insert if it believes the medication poses an increased risk in certain patient populations using the drug off-label. Beginning in 2006, Section 201.57(c) (2006) states, in part, that “A specific warning relating to a use not provided for under the ‘Indications and Usage’ section of the labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and

there is lack of substantial evidence of effectiveness for that disease or condition, and such usage is associated with serious risk or hazard.” In addition, Section 201.57(c)(3)(iii), under Indications and Usage section, states, in part, that “If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective or that the therapeutic benefits of the product do not generally outweigh its risks, FDA may require that this section state that there is a lack of evidence that the drug is effective or safe for that use or condition.”

Based on the Division Director’s memo, it is clear that FDA was well aware of the off-label use of Neurontin for neuropathic pain by at least 2002 and the agency was certainly aware of the Department of Justice’s investigation of off-label promotion on or before May 2004. At no time did FDA require a change to the Neurontin label concerning off-label uses.

Virtually all medicines have side effects. It is a well-accepted principle that neither all of the benefits nor all of the risks associated with use of a new drug will be known at the time of approval. To further evaluate the risks and benefits of a new drug after approval, FDA and the sponsor are required to monitor the medical literature, ongoing clinical investigations and adverse event reports submitted by prescribers, patients and others. This is called postmarket surveillance.

Based upon my review of the company’s postmarketing pharmacovigilance practices, including information provided by Pfizer to FDA after 2004, there was no evidence of a signal for suicide at any time following approval of the NDA in December of 1993. It also appears that no clinical information emerged during the postmarket use of Neurontin that changed the risk/benefit analysis of Neurontin for its labeled uses.

Before going into details about Neurontin, it is useful to go over some facts about the patients who take Neurontin and the conditions for which they may receive the drug. Epidemiologic data show that, in general, the patient populations participating in gabapentin trials and individuals to whom Neurontin has been prescribed after approval generally have a higher rate of suicide than people without those conditions. Because of their increased risk for suicide, clinicians expect these types of patients will have a higher suicide rate than the general population and that suicides can be expected in any clinical trial enrolling such patients regardless of treatments they may receive. **[SHOW POWERPOINT HERE (BACKGROUND SUICIDE RATES IN EPILEPSY, PAIN, AND PSYCHIATRIC POPULATIONS)].**

Regarding bipolar disorder, published data show that the rate of suicide in bipolar disorder is significantly elevated compared to the rate in the general population. One report combining the results of 28 international studies for bipolar disorder found the rate of suicide per year in that population was 4 per 1,000, compared to a background rate of 14 per 10,000 in the general population. Bipolar disorder is relatively common and is associated with elevated risks for premature death. The most significant risk for early death is from suicide. In fact, suicide rates in patients with bipolar disorder are estimated at more than 3-times higher than the risk in the general population.

Patients suffering from anxiety disorders are also at a significantly greater risk for suicide as compared to the general population. A review of the FDA database of anti-anxiety trials for a number of other drugs estimates the rate of suicide in study participants to be 0.193% per year, or about 2 suicides per 1000 people per year. This suicide rate is about 10-times greater than in the general population. Patients with depressive disorders and psychotic disorders are estimated to have a suicide risk 60-70 times higher than the general population.

Epidemiologic data also indicate that persons with chronic pain commit suicide or attempt suicide more frequently than the general population. A review of studies from 1966 through 1999 looking at the association between chronic pain and suicide reported: “Two studies [addressing completed suicide] found that the suicide rate for [chronic pain patients] is two to three times greater than the general population.” One study indicated that subjects with low back pain had a significantly increased risk of completed suicide as compared to subjects without low back pain. The studies on suicide ideation showed a very high prevalence of suicidal ideation among chronic pain patients, with a rate of suicidal ideation ranging from 17% to 66%.

Patients with epilepsy are also at an increased risk for suicide compared to the general population. Reported rates of suicide in the scientific literature concerning epilepsy estimate that up to 25% of these patients commit suicide, with an average rate of 11.5% across epilepsy populations. This is about 12 persons per 100 patients. This rate is significantly higher than the rate for the general public. Individuals with epilepsy also have higher rates of suicide attempts compared with the general population.

Based on my experience at FDA and as an FDA regulatory consultant, I am well aware of how FDA views and assesses adverse events reported after market approval of a prescription drug. I have written book chapters on this subject in textbooks and have published medical journal articles addressing adverse event reporting. Based on my review of regulatory record, it is clear to me that both the company and FDA appropriately concluded that uncontrolled data and postmarket adverse event reports are not useful in addressing a possible relationship between use of Neurontin and suicidal behavior.

Let me explain briefly about the types of data that are available in assessing the safety of a new drug. **[SHOW POWERPOINT (RANDOMIZED CONTROLLED TRIALS (RCTS))**

**AND UNCONTROLLED TRIALS)]** A randomized controlled trial (RCT) is a study in which subjects are assigned to a treatment by chance alone. The treatment can be either a sugar pill called a placebo, a known active treatment or the medicine being studied in the trial. In a double-blind RCT, neither the subject nor the physician knows which treatment or pill the patient is getting. This study design is expected to reduce bias and possible confounding factors that might obscure the effects of the experimental treatment. Double-blind, randomized, placebo-controlled clinical trials are considered the gold standard in drug development studies.

Other types of studies may be used to assess a new drug's effects. An uncontrolled study is a study in which only the experimental treatment is administered to patients and there is no comparative treatment. Uncontrolled trials may help establish the potential beneficial effects of a new drug. Uncontrolled trials may help identify the most suitable patients to include in clinical trials and may help estimate how much clinical effect can be seen with the new treatment. Following approval of the drug, adverse event reports may provide additional information associated with the use of the drug. These are generally uncontrolled data and have more limited usefulness than data from controlled trials.

When safety information is based on uncontrolled trial or postmarket adverse event reports, it is important to consider the background rate of a particular adverse event for the population of patients. In terms of safety assessments of new drugs, it is important to consider the background rate of a particular adverse event for the population of patients in whom the drug is being used. For instance, in assessing the risk of suicide in patients taking Neurontin in an uncontrolled trial, it is important to have reliable information on the background rates of suicide in patients with epilepsy, psychiatric disorders, and chronic pain. FDA epidemiologists and clinicians consider the background rates of suicidal behavior in these patient populations in

assessing the clinical importance of reports of suicidal behavior associated with the use of Neurontin. In assessing any potential association between Neurontin and any reported adverse event, including suicidal behavior, it is especially important to be able to account for confounding factors. Confounding factor can include other, coexisting medical or psychiatric conditions and other medicines used to treat those conditions

Now I would like to go over information on the development of Neurontin with you. Warner-Lambert/Parke-Davis submitted the Neurontin IND to FDA on May 29, 1986. The initial Neurontin NDA, which includes 250 volumes of data, was submitted on January 15, 1992. As part of the initial NDA review and approval process, FDA medical officers and other scientists evaluated and considered safety information available in the Integrated Summary of Safety (ISS) submitted in January 1992 and four safety updates. The ISS is the summary of all available information about the safety of the drug product, including animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations, such as data from epidemiological studies of related drugs. A Safety Update provides safety data and information from clinical trials that were not complete at the time that the NDA was submitted, and therefore were not included in the NDA submission.

The January 1992 ISS included the report of a suicide which had in a patient in one of the controlled clinical trials and which occurred six months after the patient's discontinued use of Neurontin. It is obvious that Neurontin could not have played a role in this suicide but it was reported to the agency. In addition, the ISS, which is **Exhibit 7054**, specifically addressed episodes of depression, suicidal ideation, and suicide attempt in a stand-alone section titled "Depression." This section stated that "depression is commonly reported as a concurrent illness

in the epileptic population" and that suicide attempt among epileptic patients is "estimated to be 4 to 5 times that expected in a nonepileptic population."

The FDA reviewed safety data from the Neurontin controlled clinical trials in its review of regulatory submissions from Warner-Lamber/Parke-Davis. The controlled clinical trial data show no association between Neurontin and depression. As you can see in this slide containing a table from the First Safety Update, which is **Exhibit 7068, [SHOW POWERPOINT HERE (FIRST SAFETY UPDATE)]** the controlled-trial data from the epilepsy studies reveals that 1.8 percent of Neurontin patients reported depression during experimental drug treatment compared to 1.1 percent of placebo patients. It is my opinion, and Dr. Blume agrees, that this difference in the incidence of depression, although numerically different, is not statistically or clinically different and does not demonstrate an increased risk for depression with patients assigned to Neurontin. **[SHOW POWERPOINT HERE (NEURONTIN DOES NOT INCREASE THE RISK OF DEPRESSION)]**. Had FDA reviewers concluded that Neurontin increased the risk of depression or suicide, they would have been obligated to have required a warning in the label at the time the drug was approved.

In assessing the safety and efficacy of all prescription drug products, FDA relies on the clinical judgment and expertise of its medical officers. Thus, reports of depression, suicidal behavior, and other psychiatric events were considered by FDA clinicians in their evaluation of the risk/benefit profile for Neurontin. For example, Cynthia McCormick, M.D. took notice of the suicide reported in the ISS and noted in her Medical Officer's Review of the Neurontin NDA and First and Second Safety Updates, which is labeled **Exhibit 7563**, that this suicide had occurred six months after the patient's last dose of gabapentin and that this was one suicide among the estimated 2,096 subjects exposed to gabapentin that the suicide "occurred long after

discontinuation of treatment.” As reflected on pages 102, 105, 107-09, 114, and 117 of this report, Dr. McCormick evaluated very carefully the reports of depression, suicidal ideation, and suicide attempt reported from the clinical trials. Dr. McCormick did not conclude that the clinical trial data demonstrated an increased risk for depression or suicidal behavior among the Neurontin treated patients. In fact, the First Safety Update, which Dr. McCormick reviewed and is **Exhibit 7068**, showed that there was a higher percentage of “psychobiologic events” reported for patients on placebo than those receiving Neurontin. **[SHOW POWERPOINT HERE (RATE OF PSYCHOBIOLOGIC ADVERSE EVENTS HIGHER IN PLACEBO)]**

I have reviewed in detail the Combined Medical-Statistical Review that was completed in May 1993. I would like to focus on two pages in response to Dr. Blume. First it is important to understand that at the time this document was written, the safety information was current as of September 15, 1992. **[SHOW POWERPOINT HERE (MEDICAL-STATISTICAL REVIEW DATA CUTOFF OVER ONE YEAR PRIOR TO NEURONTIN APPROVAL)]** Two more safety updates were filed by the company after this review, providing FDA with additional information on depression and suicidal behavior. On page 117, Dr. McCormick specifically addresses depression as an adverse event reported from the clinical trials. Based on the regulatory record, it is clear that Dr. McCormick continued to evaluate the safety evidence from the company’s submissions in 1993 and again in 2002 and found no basis to conclude that Neurontin was associated with an increased risk of suicidal behavior or depression.

Specifically, in 1993 Dr. McCormick reviewed the Third Safety Update submitted to FDA in May 1993 and the Fourth Safety Update submitted to FDA in December 1993. **Exhibit 7562** is Dr. McCormick’s review of the Fourth Safety Update. In her review of the Fourth Safety Update, Dr. McCormick noted that “there is a higher incidence of depression among epileptics

with partial seizures as compared to the general population.” Dr. McCormick also stated that “one cannot determine based on the available data, largely uncontrolled, whether the reports here represent an increase in incidence or intensity of depression compared to that which is expected.”

**[SHOW POWERPOINT HERE (DR. MCCORMICK’S REVIEW OF FOURTH SAFETY UPDATE)]** Dr. McCormick evaluated the full spectrum of adverse events, including episodes of depression and suicidal behavior, before concluding that Neurontin was safe and effective and should be approved for marketing.

Episodes of depression and suicide were also evaluated by Dr. McCormick's supervisor, Dr. Russell Katz. In **Exhibit 7102**, which is his Supervisory Overview report, Dr. Katz pointed out that the only suicide had occurred “after having been off drug for a considerable time.” Like Dr. McCormick, Dr. Katz did not suggest that gabapentin increased the risk for depression or suicidal behavior. Dr. Katz, who is currently the Director of the Neuropharmacological Drug Products Division, agreed with Dr. McCormick's conclusion that Neurontin was safe and effective for its intended use as adjunctive therapy for the treatment of partial seizures and should be approved. Dr. Katz's supervisor at the time, Dr. Paul Leber, Director of the Neuropharmacological Drug Products Division, agreed with Dr. Katz's and Dr. McCormick's recommendations regarding gabapentin's safety and efficacy. His report, which is **Exhibit 7107**, raised no concern about depression or suicidal behavior.

Gabapentin was the first in a new class of drugs, so it was brought before the Peripheral and Central Nervous System Advisory Committee on December 15, 1992 for their expert consideration. A transcript of this advisory committee meeting is **Exhibit 7244**. Prior to the meeting, the Advisory Committee members received a set of briefing materials, which included a draft of Dr. McCormick's Medical Officer's Review. During the course of the meeting, Dr.

McCormick provided a summary of her clinical assessment of the safety and efficacy of Neurontin. Included in Dr. McCormick's presentation was a discussion of the data on suicidal behavior and depression. Specifically, Dr. McCormick noted the suicide that had occurred six months after discontinuation of Neurontin. Dr. McCormick also noted, among other things, that there had been two suicide attempts among 2,048 clinical trial patients treated with Neurontin.

At no point during her presentation to the Advisory Committee did Dr. McCormick suggest that Neurontin causes or increases the risk for developing depression or suicidal behavior. With respect to depression, Dr. McCormick noted that "numerous examples were found on a spot check among case report forms where patients developed treatment-emergent depression, pharmacological intervention was required, and a report of a serious adverse event was not made. Indeed, it wasn't required."

After considering both safety and efficacy data, including the data on depression and suicide, the Advisory Committee voted unanimously to recommend approval of Neurontin. At no point did the Advisory Committee members suggest that there was an increased risk for suicide or suicidal ideation with Neurontin use.

FDA was very engaged with the company during the NDA review and had substantial involvement in developing the text of the Neurontin label approved on December 30, 1993. FDA correspondence and Warner-Lambert records of contact reflect at least 109 communications between Warner-Lambert and the FDA and 140 questions sent by FDA to Warner-Lambert during the FDA's review of the initial Neurontin NDA. One letter reflecting these communications, which is shown in the current slide **[SHOW POWERPOINT HERE (FDA HAD SUBSTANTIAL INVOLVEMENT IN DEVELOPING THE NEURONTIN LABEL)]**, is an approvable letter from Robert Temple, M.D., of FDA, which is **Exhibit 7029**.

FDA's significant involvement in developing the package insert is also reflected in a record of contact following a phone conversation between officials from FDA and Warner-Lambert on October 6, 1993. The record of contact, which is labeled **Exhibit 7128** and is displayed on the current slide **[SHOW POWERPOINT HERE (PRIOR TO APPROVAL, FDA CAREFULLY REVIEWED EVERY WORD OF NEURONTIN LABEL)]**, notes that FDA's delay in approving the NDA is because the agency is "fine tuning the labeling. They are reviewing every word . . . ."

At no time during the labeling discussions and conferences did FDA request or require changes to the label regarding suicide, suicidal behavior, depression, or other psychiatric-related events be modified or moved to a different frequency category. Dr. McCormick identified five potential adverse events that might limit Neurontin's widespread usefulness in her May 1993 Medical Officer's Review: Status epilepticus, potential carcinogenic effects, depression, potential nephrotoxicity, and potential teratogenicity of the drug. Three of these potential risks, nephrotoxicity, status epilepticus and carcinogenicity, were included in the warnings section of the initial Neurontin label; depression as a possible adverse event did not require a warning in the label. Depression was listed in a table discussing adverse events which occurred in the premarket clinical trials at a rate of 1% or more and occurred at a higher rate in Neurontin-treated patients than in placebo patients. Suicidal and suicide gesture also did not require a warning and were properly included in the Adverse Reactions section of the label,

I told you earlier about the standard for the addition of warnings to a drug label under 21 C.F.R. 201.57 during the relevant time frame. After reviewing all of the data for Neurontin in the NDA, FDA did not require a warning for depression or suicide in the approved label. On December 30, 1993, FDA approved the initial NDA and attached the final, approved labeling.

As noted in the FDA's approval letter, dated December 30, 1993 and labeled **Exhibit 7030**, [SLIDE] the FDA required that the final printed label be identical to the draft labeling the FDA enclosed with its approval letter. In the Neurontin label approved December 30, 1993, labeled **Exhibit 7008, [SHOW POWERPOINT HERE (FDA-APPROVED LABEL TOLD PHYSICIANS OF REPORTED SUICIDALITY EVENTS, REGARDLESS OF CAUSE)]**

“suicidal” was listed as an infrequent event and “suicide gesture” was listed as a rare event in the label’s section on adverse reactions, as shown in this slide. The approved label also properly advised physicians about the occurrence of depression in Neurontin clinical trials, which I previously said was 1.8% in Neurontin-treated patients and 1.1% in Placebo-treated patients.

**[SHOW POWERPOINT HERE (FDA-APPROVED EPILEPSY LABEL TOLD PHYSICIANS ABOUT REPORTED DEPRESSION ON NEURONTIN AND PLACEBO)]**

It is my opinion that FDA performed a careful and in-depth review of the all the Neurontin data, including data on depression and suicide. The issue of potential risks for depression and suicide was clearly on FDA’s radar early on in the process of approval. FDA asked specifically for more data on depression and suicide and Dr. McCormick addressed these issues a number of times in her Review. It is clear that FDA considered the potential adverse events of suicide and depression in its approval and labeling decisions, but did not require a labeled warning for these events.

Neurontin underwent additional regulatory review when Pfizer submitted an sNDA in August of 2001 for the management of neuropathic pain. The neuropathic pain indication was revised to post-herpetic neuralgia (PHN) in October 2001. The medical review officer for this sNDA was Sharon Hertz, M.D., and Dr. McCormick submitted her own evaluation of the PHN submission in the “Division Director Review and Basis for Approval Action.” It is clear from

the regulatory record, prior to approval FDA clinical reviewers carefully evaluated the clinical evidence for safety and effectiveness submitted in this NDA.

As with the previous NDA for the treatment of epilepsy, Pfizer's PHN regulatory submissions included data on adverse events reported during the neuropathic pain studies. In the PHN ISS dated December 13, 2001, which is **Exhibit 7087**, Pfizer provided cumulative data and patient narratives for all serious adverse events resulting in patient withdrawal from the controlled trials and for all deaths. The data from the two controlled trials in PHN and the five controlled trials for neuropathic pain indicated that more patients taking placebo reported serious depression than patients taking Neurontin. Dr. Hertz' clinical review, labeled **Exhibit 7117**, contains a table that shows the rates of depression in neuropathic pain in the neuropathic pain and epilepsy trials shown on this slide [SHOW POWERPOINT HERE (FDA FOUND A NUMERICALLY HIGHER RATE OF DEPRESSION IN PATIENTS GIVEN A PLACEBO THAN PATIENTS TREATED WITH NEURONTIN IN PAIN STUDIES)] As you can see, 1.3% of patients on Neurontin in neuropathic pain studies reported depression as an adverse event while on treatment, as compared to 2.2% of placebo patients in these studies. The other numbers are the rates of depression in the epilepsy clinical trials, which you may remember were 1.8% in Neurontin-treated patients and 1.1% in Placebo-treated patients. Neither of these differences is statistically significant. There was no reason for Pfizer to warn about depression or suicidal behavior based upon the double-blind randomized controlled clinical trials in epilepsy or neuropathic pain. Warner-Lambert also studied Neurontin in psychiatric populations. In three relatively small double-blind randomized controlled clinical trials in psychiatric patients, there was no evidence that Neurontin made depression worse.

Dr. McCormick's "Division Director Review and Basis for Approval Action" dated May 22, 2002 and labeled **Exhibit 7115** raised no concerns about depression or suicidal adverse events and states "there has been adequate demonstration of safety and effectiveness of Neurontin in the treatment of postherpetic neuralgia". Both Drs. Hertz and McCormick concluded that Neurontin's safety and efficacy in treating patients with PHN was established in two adequate and well-controlled clinical trials. On May 24, 2002, FDA approved the use of Neurontin in the management of postherpetic neuralgia, when used in accordance with the approved labeling. This May 24, 2002 approval letter is **Exhibit 7037**. Again, the approved labeling for the postherpetic neuralgia indication adequately disclosed information concerning suicidal behavior in accordance with FDA regulatory requirements.

In December 2005, Pfizer agreed to update the Neurontin package insert by replacing the terms "suicidal" and "suicide gesture" with the terms "suicide attempt" and "suicide". These changes are reflected in **Exhibit 7026**, which is the December 2005 Neurontin label. FDA considered these changes to be "minor," as you can see in the current slide. **[SHOW POWERPOINT HERE (FDA'S 2005 'MINOR' CHANGE TO SUICIDE-RELATED ADVERSE EVENT TERMS IN NEURONTIN'S LABELING)]** This is the November 22, 2005 email from FDA requesting the labeling change, which is **Exhibit 7204**. The original terms "suicidal" and "suicide gesture" had been approved by FDA based on a modification of the standard adverse event coding dictionary used both by FDA and pharmaceutical companies marketing drugs in the U.S. The Neurontin labels containing these terms were adequate for the purpose of putting prescribers on notice about potentially "suicidal" adverse events reported from the clinical trials. In 2005, this minor labeling change updated the clinical adverse event terminology in the Neurontin label, but did not change the label in any significant way. These

changes in terminology are analogous to an old way of referring to persons with epilepsy as having “fits” or “epileptic fits” instead of the more current terminology “seizures” or “epileptic seizures”. The older or archaic terminology is “epileptic fit” and the newer term is “epileptic seizure”. These terms basically have the same meaning to a clinician; it is just that the term “seizure” is the currently preferred terminology. The changes in labeling terminology for Neurontin are similar to the changes in the way we refer to the clinical manifestations of epilepsy.

It is my opinion that the Neurontin package inserts before and after December 2005 adequately informed prescribers of the risks and benefits of Neurontin, particularly with respect to suicide-related events. For these reasons, I believe the Neurontin package insert at all times relevant to this litigation adequately and appropriately disclosed the potential risks of suicidal thinking and behavior in patients taking Neurontin.

In June of 2006, at the request of the FDA and using FDA inclusion criteria, Pfizer submitted the results of its evaluation of Neurontin clinical trial data for “possibly suicide-related adverse events.” This submission from June of 2006 is labeled **Exhibit 7207**. This submission only included data from controlled clinical trials, the most appropriate data for this type of analysis. One example of the FDA’s perspective on the use of clinical trials data for this type of analysis is **Exhibit 7209**, which is an April 12, 2005 letter from Dr. Katz of the FDA to Andrew Finkelstein of the Finkelstein Law Firm. Prior to this letter, the Finkelstein firm had been submitting adverse event reports to FDA that they claimed involved Neurontin and suicidal behavior. FDA makes it clear that uncontrolled adverse event data on suicide are not useful in evaluating whether Neurontin was associated with an increased risk for suicidal behavior. Specifically, as you can see in this slide **[SHOW POWERPOINT HERE (FDA:**

**CONTROLLED TRIALS ARE ONLY WAY TO ASSESS WHETHER NEURONTIN IS ASSOCIATED WITH INCREASED RISK OF SUICIDE]**, in 2005 FDA told lawyers in the Finkelstein firm that “these illnesses are well-known to be associated with an increased risk of suicide compared to the general population. Further, in the absence of an appropriate control group, it will be difficult, if not impossible, to assess the role of any other factors that might explain these events, such as concomitant medications.” This statement by FDA supports one of my major objections to Dr. Blume’s opinion – although FDA advised the plaintiffs’ lawyers that uncontrolled data was not appropriate to analyze suicidal behavior, her report spends dozens of pages relying upon uncontrolled data.

FDA has also commented specifically on the use of spontaneous adverse event data to analyze suicidality. In an April 1, 2008 email to Dr. Alex Ruggieri, which is labeled **Exhibit 7392** and shown on this slide, **[SHOW POWERPOINT HERE (FDA: CONTROLLED TRIAL DATA ARE THE ONLY WAY TO ESTABLISH WHETHER AEDS ARE RESPONSIBLE FOR SUICIDE)]**, FDA stated:

Concerning your question why data from the FDA Adverse Event Reporting System (AERS) has not been analyzed or made public, the agency does not believe that spontaneous post-marketing reports can be interpreted appropriately in this situation. Patients taking these drugs have a high background rate of suicidal thoughts/behaviors, and it is not possible to tell from AERS reports, whether the drug caused them. In the agency’s view, the only way to establish whether or not the drugs are responsible for suicidality is to analyze controlled trial data.

FDA commented on the use of spontaneous adverse event data to assess suicidality associated with Neurontin for a third time at the July 10, 2008 Joint Meeting of the Peripheral and Central Nervous System and Psychopharmacologic Drugs Advisory committees. A transcript of this meeting is labeled **Exhibit 7257**. At this Joint Advisory Committee Meeting, as shown in the current slide **[SHOW POWERPOINT HERE (FDA: USE PLACEBO-**

**CONTROLLED TRIALS BECAUSE POSTMARKETING DATA ARE UNINTERPRETABLE]**, Dr. Russell Katz of FDA stated, "...we had long ago decided that postmarketing data are not the right data to look at, or we don't believe that these sorts of things where there is a high background rate of suicidality so defined in these populations, I think that we have concluded that postmarketing data is uninterpretable, and that is why we went to placebo-controlled trials."

Getting back to the June 2006 submission, this analysis included 8829 patients, in which 336 cases of "possibly suicide-related" adverse events were identified. Further review of the 336 possible cases suicide-related adverse events associated with Neurontin use revealed zero actual cases of completed suicide, zero cases of attempted suicide, and zero cases of "preparatory acts towards imminent suicidal behavior" in the data set. The incidence of suicidal ideation which is another term for suicidal thinking among Neurontin users was nearly identical to that of placebo patients, specifically 3.9 per 10,000 in Neurontin patients and 3.7 per 10,000 in placebo patients. **[SHOW POWERPOINT HERE (CONTROLLED TRIALS: NO INCREASED RISK OF SUICIDE WITH NEURONTIN)]** Pfizer wrote, "[T]he currently submitted data provides further support for the conclusion that Neurontin neither causes nor is associated with an increased risk of suicidal behavior and thinking, including completed suicide, suicide attempt, suicide gesture and suicide ideation." Thus, these data do not demonstrate an increased risk for suicide or suicidal behavior in patients treated with Neurontin as compared to patients treated with placebo.

As you can see depicted in the slide currently being shown **[SHOW POWERPOINT (EVALUATIONS OF DEPRESSION AND SUICIDALITY)]**, after numerous evaluations of

data on depression and suicidality, neither FDA nor the Company detected a signal for increased depression or suicidality based on Neurontin data alone.

Following the company's submission of the controlled clinical trial data in 2006, FDA included the Neurontin clinical trial data on suicidality in its own analysis, along with controlled clinical trial data for 10 other antiepileptic drugs, or AEDs. This 2008 FDA analysis is labeled **Exhibit 7559**. FDA concluded that all AEDs, including those not represented in this analysis, and including drugs not yet approved as AEDs, will be required to put suicide-related warnings in their labels. The FDA analysis was not designed to establish whether any particular AED, including Neurontin, is associated with an increased risk for suicide, but rather is the AED class of drugs associated with an increased risk for suicide. The question concerning whether there was an increased risk for each individual AED was raised during the July 2008 Joint Advisory Committee meeting. The FDA statistician, Dr. Levenson, confirmed that the combined analysis demonstrating an increased risk for suicide required the entire data set from all 11 AEDs which you can see on the slide that is currently being shown. **[SHOW POWERPOINT HERE (FDA META-ANALYSIS – ENTIRE DATA NECESSARY TO DRAW CONCLUSIONS)]** Dr. Twyman, a member of the advisory committee, asked: "Let's assume that the effect is generalizable to the class of AEDs. But if you look at the compounds individually, could one draw the conclusion individually that compounds have a risk, or do you need to the entire data set of all the AEDs put together in order to draw the conclusion that AEDs have a signal?" Dr. Levenson, an FDA statistician, replied: "I would say we need the entire data set in this case."

After the Joint Advisory Committee Meeting, FDA instituted class labeling for AEDs. Class labeling is specific language FDA requires be included in the labels of all drugs within a certain class or type of medicines. Class labeling usually addresses a risk that FDA believes is

shared by all medicines in that class of drugs. A class can be a pharmacologic class, where the drugs share a similar mechanism of action, or it may be a therapeutic class, where drugs with different mechanisms of action are used to treat a particular condition. From Neurontin's initial approval 1993 up through early 2009, FDA did not require a warning for suicide or depression in the Neurontin label based on Neurontin data alone. I concur -- there was no scientific or medical basis for such a warning. Only FDA can mandate a class warning and only FDA had access to all the data on which it based the 2009 class labeling for AEDs.

FDA has not concluded that AEDs cause suicide or suicidal behavior. In **Exhibit 7558**, a December 2008 alert on suicidal behavior, suicidal ideation and antiepileptic drugs, shown in the current slide, **[SHOW POWERPOINT HERE (DECEMBER 16, 2008 – FDA TO PHYSICIANS: FDA HAS NOT CONCLUDED AEDS CAUSE SUICIDAL BEHAVIORS]** FDA stated that its analysis does not mean that it has concluded that there is a causal relationship between AEDs and suicidal behavior, and that FDA is not advising physicians or patients to discontinue appropriate prescribing of AEDs.

I have reviewed the report submitted by plaintiffs' retained expert, Cheryl Blume, Ph.D., as well as her deposition testimony. There are a number of errors and misconceptions in both her expert report and in her testimony at deposition. Dr. Blume refers to "Regulatory documents from the FDA" as reflecting Pfizer's knowledge about safety issues related to Neurontin. The document from which Dr. Blume quotes is the Medical and Statistical Review from the initial approval of Neurontin as adjunctive treatment in refractory partial seizures with and without secondary generalization in adults with epilepsy. Scientific reviews like this are archival documents intended to record the medical and statistical reviewers' bases for their recommendations for regulatory actions such as marketing approval. The FDA's final decisions

about the safety and effectiveness of an approved new drug are provided to the sponsor in the approval letter and the approved labeling. Dr. Blume is mistaken if she believes that the MOR reflects FDA's final assessments of safety and effectiveness of a drug product. The MOR is not routinely provided to a sponsor as a "regulatory document". In fact, that specific MOR was only available via a Freedom of Information request at the time of initial approval.

Dr. Blume also alleges that Pfizer failed to include information in the Neurontin label about the effects of gabapentin on monoamine neurotransmitters within the central nervous system. A review of the draft labels submitted to FDA by Warner-Lambert prior to the initial approval of Neurontin indicates that this allegation misrepresents the facts. The January 1992 draft label submitted with the Neurontin NDA, which is **Exhibit 7004**, includes this statement by Warner-Lambert in the Mechanism of Action section: "Gabapentin slightly reduces the release of monoamine neurotransmitters *in vitro*." This sentence appears in a number of subsequent drafts of the product label before FDA deleted it in December 1993.

Similar language about Neurontin's possible mechanism of action was included in the draft label submitted with the PHN NDA. The draft labels Warner-Lambert provided to FDA in August 2001 and January 2002 included the statement: "Gabapentin reduces the stimulated release of noradrenaline, dopamine, and glutamate under laboratory conditions. Gabapentin administration to humans increases the total brain content of GABA after a single dose. However the relevance of these findings to clinical use is not yet clear." Again FDA deleted this language from the draft package insert prior to Neurontin's approval for treatment of post-herpetic neuralgia. It is my opinion that FDA would not have removed this language if FDA scientists and clinicians believed it had any relevance to the safe or effective use of the product. I believe Dr. Blume is mistaken in her assertion that Neurontin's possible effects on

neurotransmitters in the central nervous system has any bearing on the safety of Neurontin, an opinion that is supported by FDA's deletion of this language from the Neurontin labels. After May of 2002, there has been no reason, or scientific basis, for Pfizer to resubmit similar labeling to FDA on this issue.

I have reviewed the reported methods and data upon which Dr. Blume appears to base the opinions she offers in her report. At a number of places in her report, Dr. Blume presents what are essentially line listings of adverse events and clinical trial withdrawals, and then draws inferences and conclusions from those line listings. I see no evidence that she performed any analyses to determine if the differences she claims to have identified in rates of events between the comparison groups (Neurontin-treated patients or placebo-treated patients) are likely to be real differences or differences due to chance alone. The types of comparisons she makes, simply comparing counts of events in the Neurontin-exposed population to counts of similar events in a placebo-exposed population do not constitute reliable evidence of differences between the Neurontin-exposed population and the placebo-exposed population, much less evidence of causation. The "analyses" she reports are not consistent with generally accepted epidemiological principles and are not reliable as estimates of an association between those events and the exposures of interest. Such simple comparisons are not used by epidemiologists, clinical scientists or regulatory agencies, such as FDA, to evaluate whether a medicine is causally associated with an adverse event. Dr. Blume's lists of adverse events do not contribute to the scientific assessment of a possible association between Neurontin and suicide. Dr. Blume's analyses involve nothing more than eye-balling counts of various adverse events, which is not a valid scientific assessment of risk. Dr. Blume opines that reports of positive "dechallenge" and "rechallenge" support for her claims that Neurontin plays a causal role in suicide or suicidal

behavior among patients exposed to the drug. A positive dechallenge is when a suspect drug is withdrawn and the particular adverse event regresses or disappears. A positive rechallenge means the suspect drug is re-introduced and the adverse event recurs. Dechallenge and rechallenge are most meaningful when the adverse event is an objectively documented or measured event, such as abnormal kidney function tests. In this instance, positive dechallenge and rechallenge occur when the kidney function tests improve with discontinuation of the suspect drug and then become abnormal again when the drug is re-introduced. Dechallenge and rechallenge data are not useful in subjectively reported events such as depression. The highly subjective dechallenge and dechallenge/rechallenge events like several of those cited by Dr. Blume, are subject to biases which render them more difficult to interpret than changes in objective adverse events like laboratory or blood tests. Dr. Blume's use of positive dechallenge to support her opinions about Neurontin is misleading because positive dechallenge for those same events occurred in placebo patients in the same Neurontin clinical trials. Also, the draft and final of Dr. McCormick's Medical-Statistical Review addressed the dechallenge and rechallenge events that Dr. Blume relies upon, and she did not attach any significance to those events nor did she recommend any language in the labeling based on those events.

In addition, the "psychobiological" events discussed by Dr. Blume are not rare in the patient populations exposed to Neurontin in the absence of Neurontin exposure and have no documented predictive value for suicide or suicidal behavior.

Dr. Blume testified at her deposition that the Neurontin package insert should have contained warnings or other labeling changes that would discourage physicians from prescribing Neurontin based on safety issues she has identified. She also noted in her report that Pfizer

should have warned healthcare professionals about a possible lack of efficacy in certain off-label indications. I do not agree with these opinions.

Dr. Blume testified that FDA has known for several years that physicians were prescribing Neurontin for off-label indications. First, FDA does not regulate the practice of medicine, meaning that once a product is approved for marketing in the U.S., prescribers are permitted to prescribe the product however they feel is in their patients' best interests. Furthermore, if FDA had information indicating that a specific off-label use provided no benefit to patients, FDA could have required a statement in the label to that effect. More recently, FDA has had the authority to require Pfizer to include a specific warning in the labeling addressing efficacy or safety concerns associated with off-label uses. To date, FDA has not requested any changes addressing off label uses in the Neurontin labeling and it is my opinion that no such changes are necessary or appropriate based on the available clinical data.

Dr. Blume's report sets forth a purported "Proportional Reporting Rate" ("PRR") of the FDA AERS database in support of her contention that the postmarketing surveillance data revealed a "signal" for suicide. The analysis presented in Dr. Blume's report is not a PRR. Rather, Dr. Blume merely presents the percentage of suicide events for each drug relative to the total number of adverse events for that drug. This is not the generally accepted method for calculating a PRR, which would require an analysis of the entire AERS database. Even if her analysis were a generally accepted-type of PRR, Dr. Blume has not followed generally accepted methodology in interpreting the information. As stated by Dr. Brian Strom (who Dr. Blume has acknowledged as an authority in the field of pharmacoepidemiology) in a 2005 article that is labeled **Exhibit 987**, "...true signals should emerge from clinical judgment and that statistical algorithms, such as PRRs, should be used as supplements to clinical and epidemiological

judgment, not replacements.” PRRs and the adverse event reports used to calculate them are hypothesis-generating only. Spontaneous adverse event reports are voluntary reports of possible adverse effects of medications submitted to FDA or the manufacturer by healthcare providers, patients, and other interested parties. These reports are often subjective and generally are only useful in generating signals of possible new safety information,

Dr. Blume is not qualified to assess clinical adverse event data in a meaningful way. She is neither a clinician nor an epidemiologist and does not have the appropriate qualifications to interpret clinical or epidemiological data in evaluating her purported PRR results.

Dr. Blume further asserts in her declaration that by the fourth quarter of 2002, increases in reports of serious adverse events were due to increases in off-label use. As she acknowledged in her first deposition, notoriety bias during this time period would likely increase reporting rates of adverse events. Dr. Blume apparently failed to recognize the general increase in reporting of suicides to FDA’s Adverse Event Reporting System during this time period, including published reports of suicide by Poison Control Centers. Failure to account for these variables significantly limits the reliability of the inferences Dr. Blume makes simply using counts of adverse events.

Plaintiffs have suggested that a combination of information (“red flags”), when considered together, provides sufficient evidence that Neurontin has the biologic capacity to cause suicidality and that the Neurontin label should have been changed to include a warning pertaining to suicidality. First, much, if not all, of this information was submitted to and considered by FDA during review and approval of this product. Specifically, information pertaining to dechallenge/rechallenge events, spontaneous adverse event reports, and safety data included in the NDA, sNDAs, Safety Update Reports and other safety submissions, did not suggest that Neurontin was associated with suicidality. In the absence of data signaling a risk for

suicidality, warnings in the labeling were neither appropriate nor required. I have addressed many of the problems with this evidence in my testimony and reports in this litigation.

For example, the suggestion that detailed information submitted to FDA about patients who withdrew from clinical trials due to adverse events constituted a signal of suicidality is baseless. First, at the time the data were submitted, FDA reviewed the information about these patients and did not conclude that there was a signal for suicide or suicidality. Second, there is no scientifically accepted connection between the various adverse event terms cited by Dr. Blume and a risk for suicide or suicidality. Third, the various tables setting forth clinical trial withdrawals are incomplete and, when appropriately configured, do not demonstrate any consistent pattern signaling a risk of suicide or suicidality among Neurontin users. Moreover, the use of Dr. Blume's purported PRR analysis of adverse event terms from various adverse event databases is not scientifically valid and, in my opinion, does not demonstrate a signal for suicidality. Finally, the FDA alert and subsequent meta-analysis do not in any way mean that Pfizer's Neurontin label was inadequate in its portrayal of the risk of suicide or suicidality.

**[SHOW POWERPOINT HERE (BLUME'S "RED FLAGS" HAVE NO CREDIBILITY)]**

I also have an opinion on advertising for medicines as it relates to this case. I have expertise in this area. I have experience in providing information to the public on approved and unapproved medications through my work in the Office of AIDS and Special Health Concerns and am very familiar with the regulations addressing labeling, advertising and promotion of prescription medicines.

The FDA monitors prescription drug advertising through DDMAC, the division at FDA responsible for reviewing, evaluating, and commenting on advertising, presentations and written materials provided to prescribers as well and any other promotional statements or materials.

DDMAC's mission is “[t]o protect the public health by assuring prescription drug information is truthful, balanced, and accurately communicated.” DDMAC basically enforces labeling regulations as applied to advertisements. These regulations require advertisements for a prescription drug include a brief summary of information about the drug, such as side effects, contraindications, and effectiveness that is consistent with the approved product label. This summary should be a “true statement” of information about important risks and benefits, which is provided in a balanced fashion so that effectiveness claims are balanced with information about side effects, about specific conditions under which the drug’s benefits do not outweigh possible risks, and information about known or potential side effects. An advertisement or other promotional material may be considered false and misleading by a DDMAC reviewer if he or she determines that the risks and benefits of the product are presented in a way that “lacks fair balance.” The specific allegations of “false and misleading,” “lacking in fair balance,” or “failing to provide a true statement” of risks and benefits are required in all letters or other contacts between DDMAC and the product sponsor when notifying the sponsor of possible regulatory violations. Although the regulations provide some guidance on what constitutes a “true statement,” “fair balance,” and “false and misleading,” application of the regulations is subjective.

DDMAC reviews all “launch materials” used for advertising at the time of the initial approval or when additional indications are approved by FDA. These advertising materials come directly from the pharmaceutical manufacturer and are reviewed by pharmacists, lawyers, nurses, and other trained personnel in DDMAC. Often, the people in DDMAC reviewing these materials are assigned to products in a specific therapeutic class, so they are familiar with the claims and concerns associated with that specific type of medicine..

If a DDMAC reviewer believes an advertisement violates FDA regulations, there are a number of responses he or she may initiate. Among these possible responses are, in increasing order of severity: untitled letters, warning letters, recalls, seizures, injunctions, administrative detention, and criminal prosecution. Sending an untitled letter to a sponsor is the lowest level of response to a potential regulatory violation. The CDER handbook, a document produced by FDA to explain its policies and procedures for reviewers, notes that an untitled letter is used to “address promotion violations that are less serious than those addressed in warning letters.” “There is no requirement that the agency take enforcement action, although the [untitled] letters may serve as a basis for additional regulatory action.”

Pfizer received a letter from DDMAC on June 29, 2001 and on July 1, 2002. In response to the June 29, 2001 letter, not only did Pfizer withdraw all promotional materials with references to the study cited by DDMAC, but it also reviewed additional promotional materials for mentions of other studies similar in design to the study to which DDMAC objected. Pfizer provided its initial response to DDMAC within the specified 10-day timeframe. Pfizer also told DDMAC they were discontinuing the use of the materials cited in the letter and were looking for other advertising and promotional materials that might be objectionable because they included statements or claims based on similar types of studies. These were timely and appropriate responses by Pfizer and resulted in withdrawal of the specific materials cited by DDMAC as well as other materials similar to the ones cited. No additional regulatory actions were taken following Pfizer’s responses to the DDMAC letter, even though there were other options DDMAC could have pursued had DDMAC considered Pfizer’s response to the letter unsatisfactory. As far as the July 1, 2002 letter is concerned, the issues raised about this piece which DDMAC termed “misleading” are minor issues. Importantly, the term “misleading” does

not mean that any physician or consumer was actually misled. Also, DDMAC did not require Pfizer to issue a retraction or propose a corrective action to address the concerns noted in the letter.

So to reiterate my opinions in this matter, it is my opinion: **[SHOW POWERPOINT HERE (SUMMARY OF DR. ARROWSMITH'S OPINIONS)]** First that the Neurontin labeling was adequate under the regulations and provided appropriate information for safe and effective use. Second that the package insert, and the Investigator's Brochure prior to approval, included information concerning suicidal behavior and adverse effects on mood reported during clinical testing. And third that there was no reason for Pfizer to warn of suicidal behavior in the Neurontin labeling prior to the requirement of class labeling in 2009 as the available information did not establish that this medicine was associated with an increased risk of suicidal behavior.